Population Pharmacokinetic Analyses for Belzutifan to Inform Dosing Considerations and Labeling

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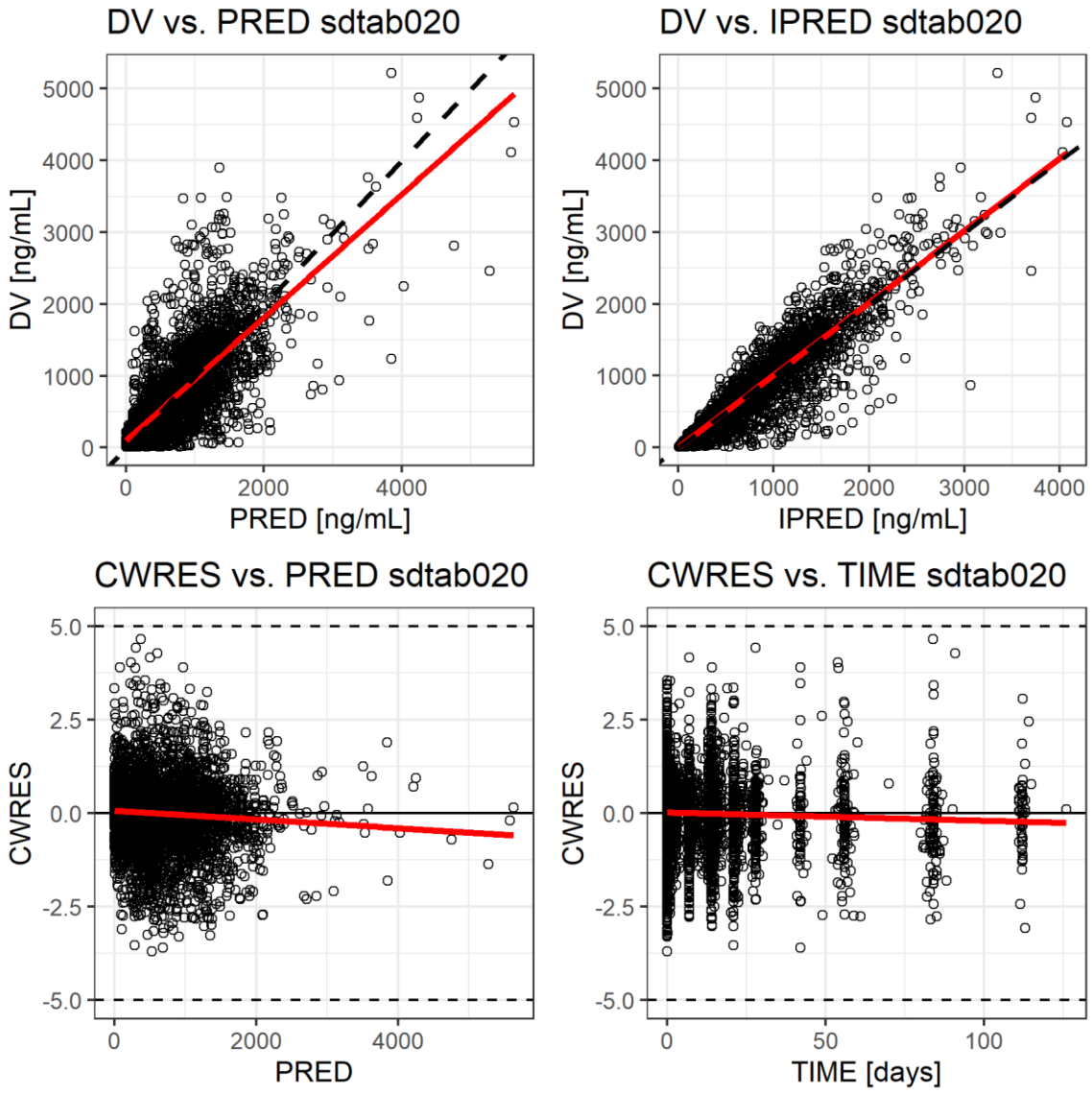
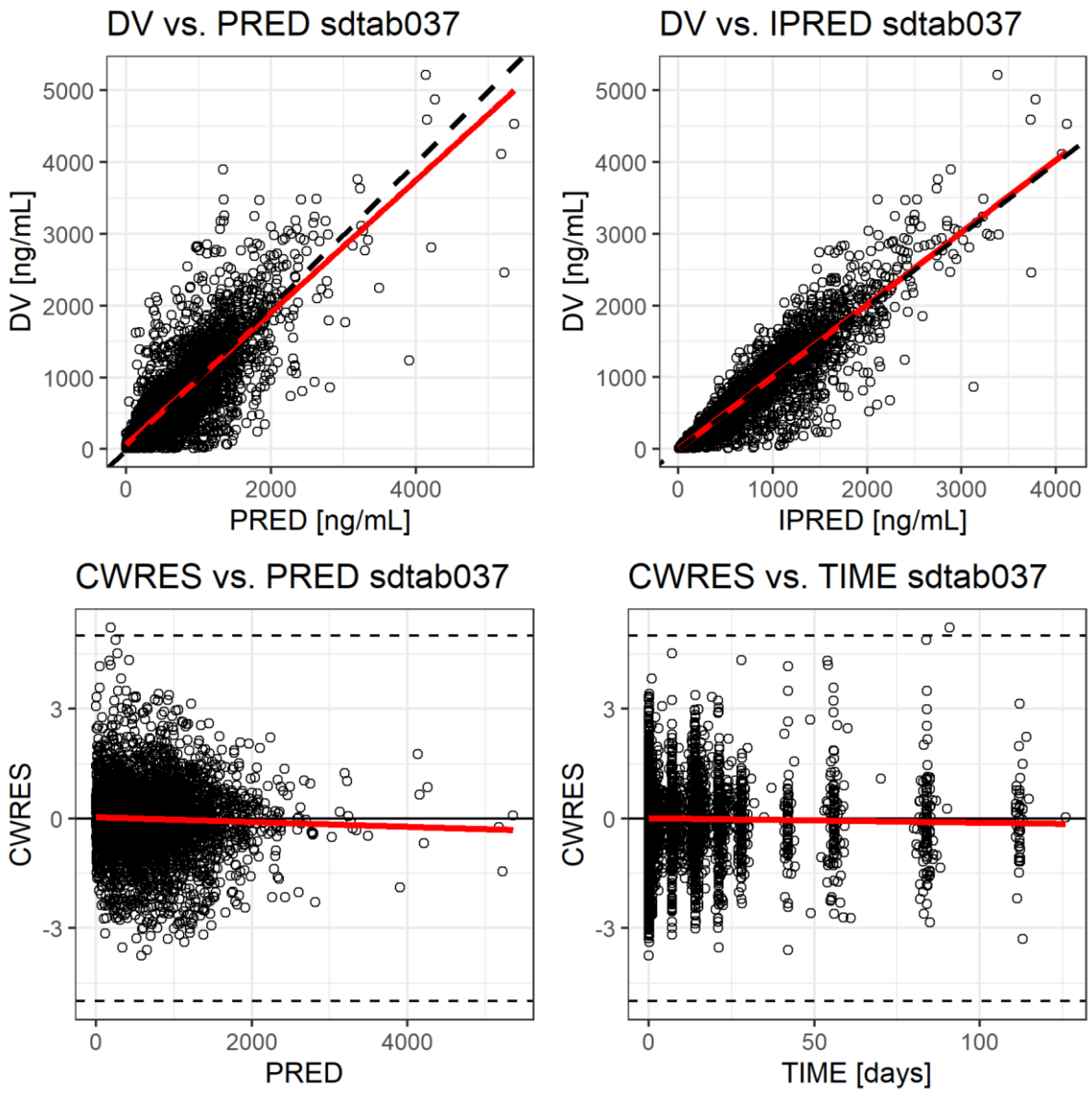
Figure S1. GOF Plots for the Base Model (A) and the Final Model (B)

A



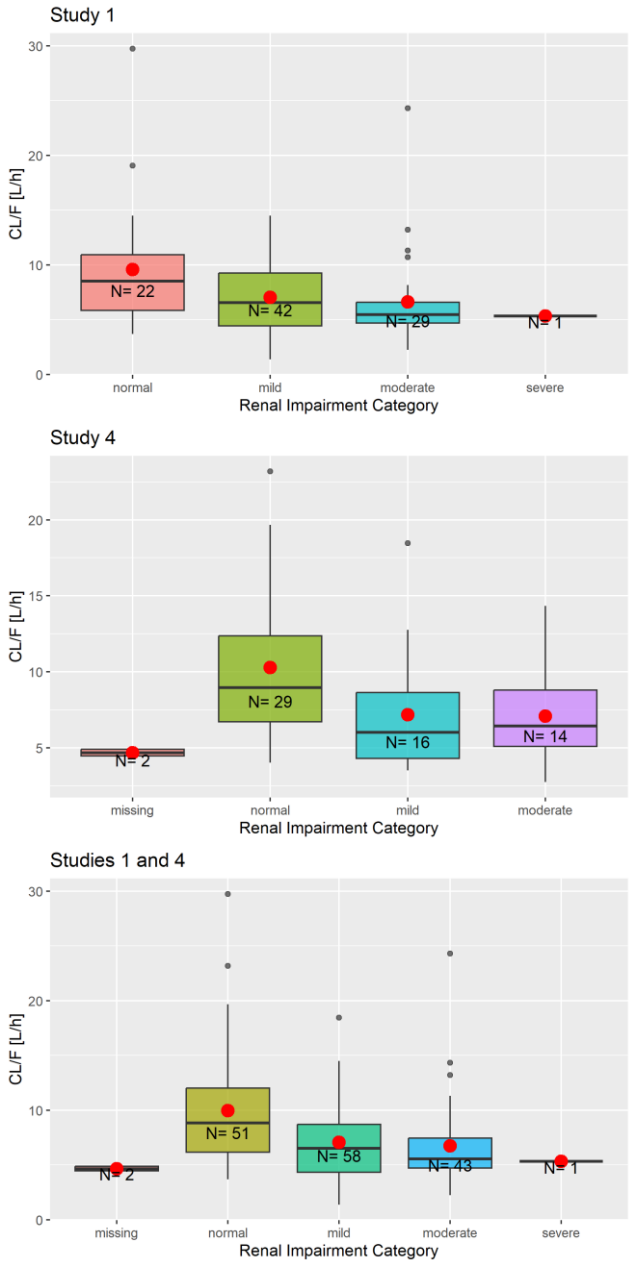
B



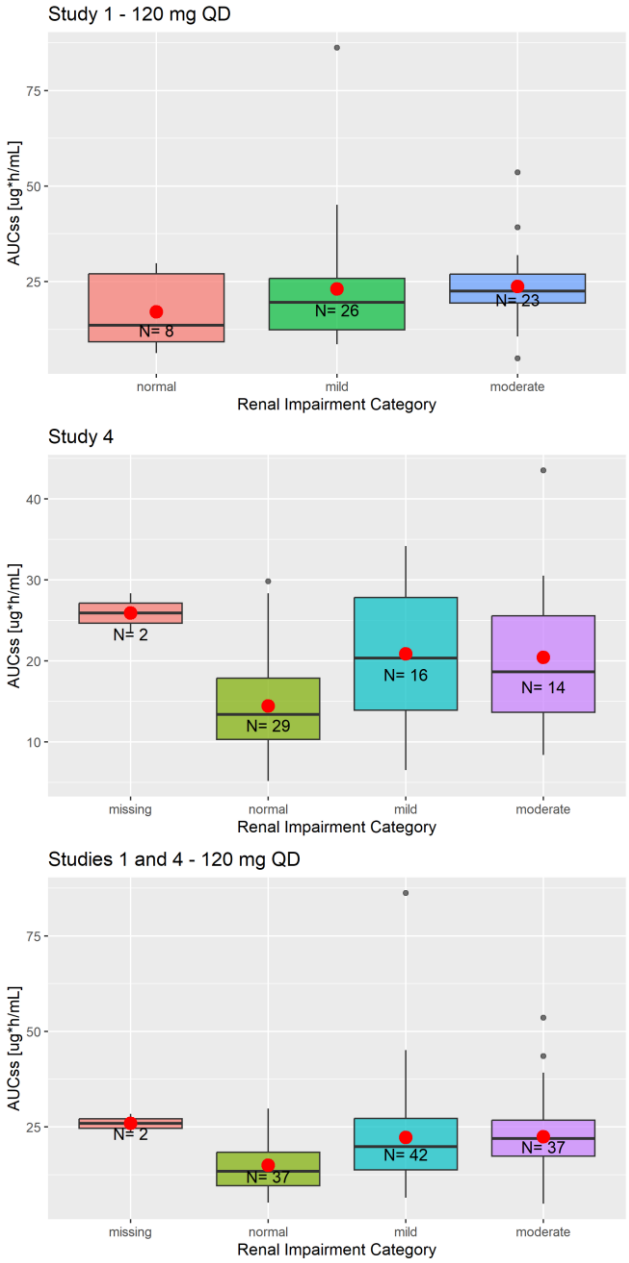
Notes: Dots are individual data points and red lines are linear regression lines. In the two plots in the upper row, dashed black lines are lines of identity, while in the two plots in the lower row, dashed lines show the boundaries of the CWRES ± 5 interval.
Abbreviations: CWRE, conditional weighted residuals; DV, dependent variable (usually observation); GOF, goodness-of-fit; IPRED, individual predictions; PRED, population predictions.

Figure S2. Apparent Clearance (A) and AUC at Steady-State (B) by Renal Impairment Category and Apparent Clearance (C) and AUC at Steady-State (D) by Hepatic Impairment Category

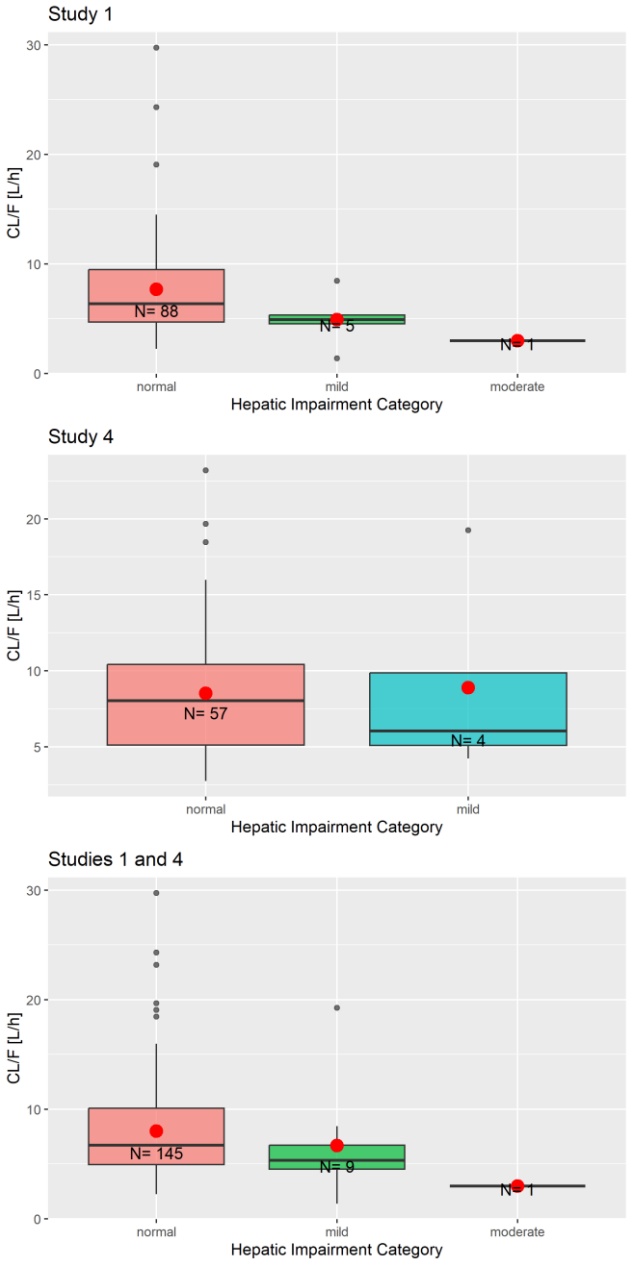
A



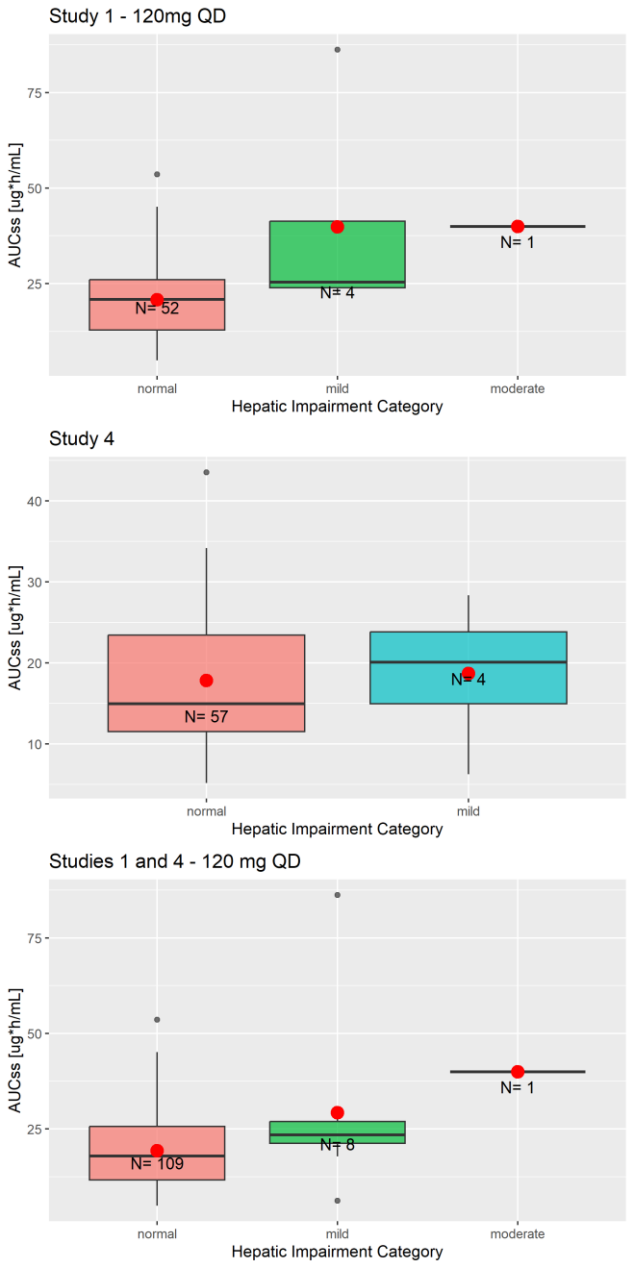
B


Study 1 - 120 mg QD
AUCss [ug*h/mL]
75
50
25
N= 8
N= 26
N= 23
normal
mild
moderate
Renal Impairment Category
Study 4
AUCss [ug*h/mL]
40
30
20
10
N= 2
N= 29
N= 16
N= 14
missing
normal
mild
moderate
Renal Impairment Category
Studies 1 and 4 - 120 mg QD
AUCss [ug*h/mL]
75
50
25
N= 2
N= 37
N= 42
N= 37
missing
normal
mild
moderate
Renal Impairment Category

C


Study 1
CL/F [L/h]
30
20
10
0
N= 88
N= 5
N= 1
normal
mild
moderate
Hepatic Impairment Category
Study 4
CL/F [L/h]
20
15
10
5
N= 57
N= 4
normal
mild
Hepatic Impairment Category
Studies 1 and 4
CL/F [L/h]
30
20
10
0
N= 145
N= 9
N= 1
normal
mild
moderate
Hepatic Impairment Category

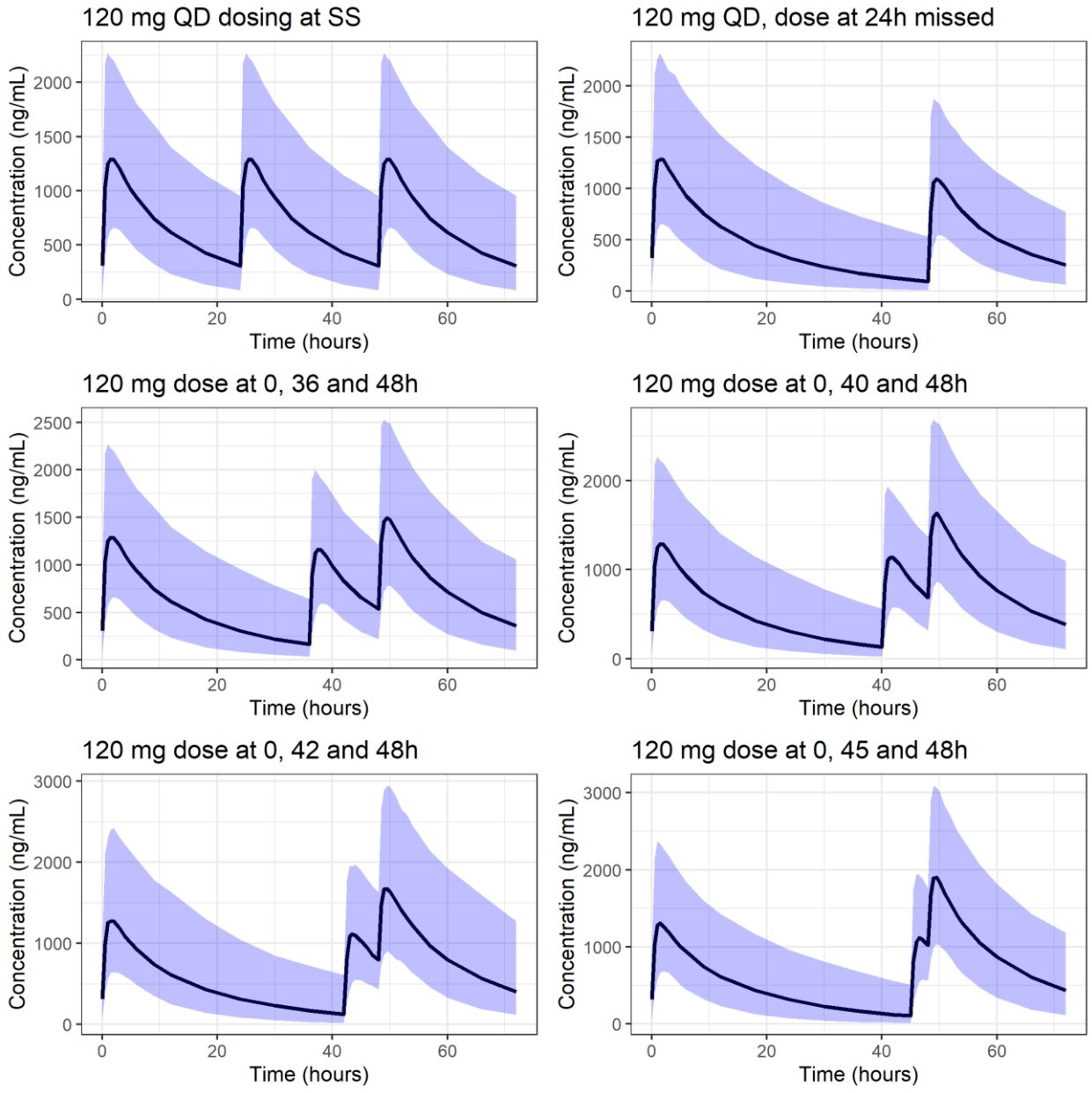
D



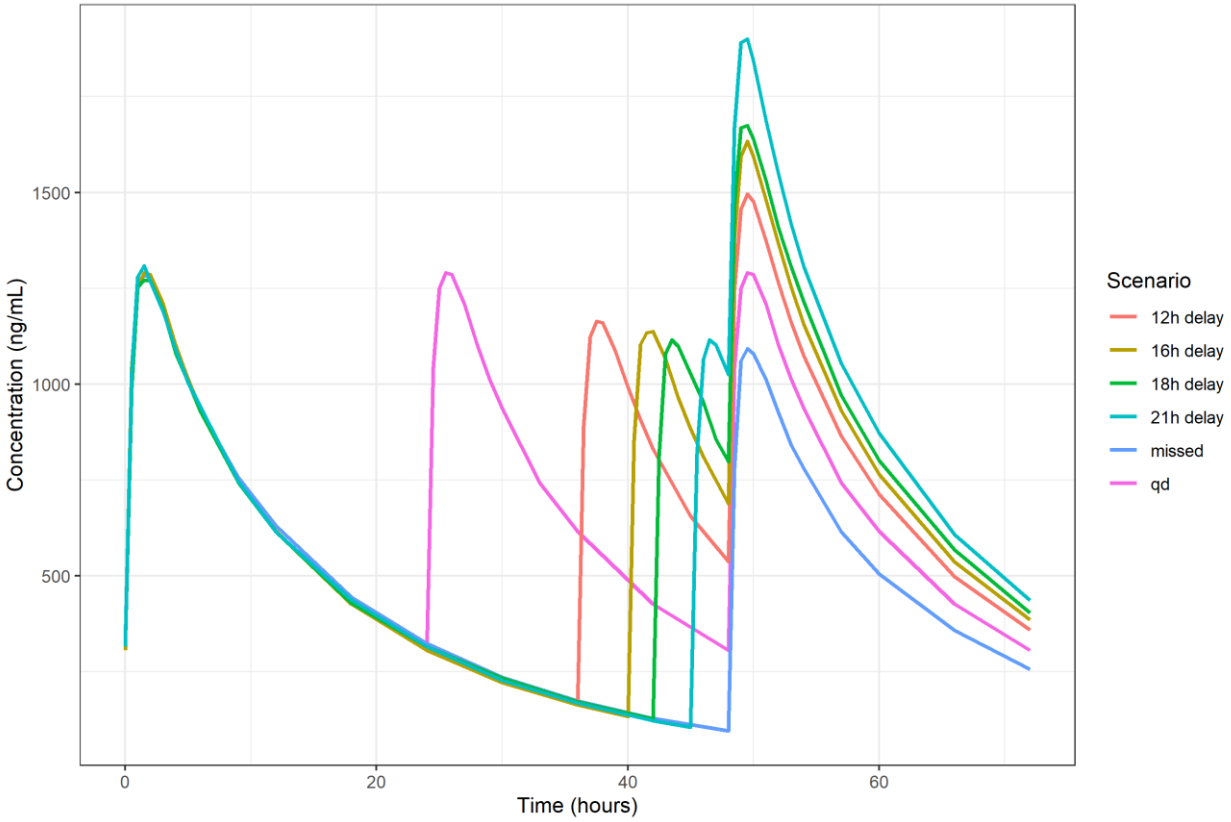
Notes: Boxplots show the 25% (Q1, lower end), 50% (median, middle line) and 75% (Q3, upper end) percentiles of respective data by group. Lower whiskers indicate the lowest observed value within [0.5*Q1, Q1], and upper whiskers indicate the highest observed value within [Q3, 1.5*Q3]. Red points shows the mean values by group. Black points are outliers. (B) For combined Study 1 and Study 4 patients dosed with 120 mg QD, the geometric mean (geometric CV%) of post-hoc nominal AUCss for patients in normal, mild and moderate renal impairment categories were 13.35 (52.24%), 19.21 (57.99%) and 20.41 (48.91%) µg.h/mL, respectively. Overall, the geometric mean AUCss were 1.44-fold and 1.53-fold in mild and moderate renal impairment categories, respectively, compared to the normal category. (D) For combined Study 1 and Study 4 patients dosed with 120 mg QD, the geometric mean (geometric CV%) of post-hoc nominal AUCss for subjects in normal and mild hepatic impairment categories were 17.06 (53.92%) and 23.34 (81.72%) µg.h/mL, respectively. Overall, the geometric mean AUCss was 1.37-fold in mild hepatic impairment category compared to the normal category
Abbreviations: AUCss, area under the plasma concentration-time curve at steady-state; N, number of patients; Q1, first quantile; Q3, 3rd quantile; QD, once daily

Figure S3. Impact of Missed or Delayed Doses on Belzutifan Exposure (A) and Comparison of Median PK Profiles for Missed or Delayed Dosing Scenarios (B)

A



B



Notes: Simulations were performed to assess the impact of missed or delayed doses on belzutifan exposure. Concentration-time profiles at 72 hours were simulated with observations at 0, 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 18, 24 hours after each dose, and thereafter every 6 hours until the next dose. The covariates from the Study 4 population (61 patients) were used 10 times to generate 610 virtual patients. Resulting concentration-time profiles (A) and the medians of all scenarios overlaid are shown. AUC, Cmax and Cmin by scenario (B) are shown.
Abbreviations: AUC, area under the plasma concentration-time curve; Cmax, maximum plasma concentration; Cmin, minimum plasma concentration; PK, pharmacokinetics; QD, once daily; SS, steady-state.
The following dose scenarios were evaluated:

- Scenario 1: doses at 0 (SS assumed), 24, and 48 hours
- Scenario 2: doses at 0 (SS assumed) and 48 hours; second dose missed
- Scenario 3: doses at 0 (SS assumed), 36, and 48 hours; second dose 12 hours delayed
- Scenario 4: doses at 0 (SS assumed), 40, and 48 hours; second dose 16 hours delayed
- Scenario 5: doses at 0 (SS assumed), 42, and 48 hours; second dose 18 hours delayed
- Scenario 6: doses at 0 (SS assumed), 45, and 48 hours; second dose 21 hours delayed

Table S1. Base Model Parameter Estimates

Parameter	Estimate	% Relative SE	Asymptotic 95% CI	% Shrinkage
Fixed Effects				
CL/F (L/h)	5.85	3.46	5.45; 6.25	--
V2/F (L)	84.77	3.37	79.17; 90.38	-
Q/F (L/h)	5.47	16.38	3.71; 7.22	--
V3/F (L)	30.21	7.97	25.49; 34.93	--
KA (/h)	1.91	10.83	1.50; 2.32	--
ALAG (h)	0.16	1.74	0.16; 0.17	--
KA-FED	-0.87	8.91	-1.02; -0.72	--
CL-WT	1.05	9.8	0.85; 1.26	--
V-WT	1.08	3.63	1.00; 1.15	--
Random Effects				
IIV on CL/F	0.27	10.05	0.22; 0.33	0.58
IIV on V2/F	0.016	24.13	0.0085; 0.024	24
IIV on V3/F	0.19	34.3	0.061; 0.31	27
IIV on KA	1.10	12.86	0.82; 1.37	15
Residual Error				
RES HV	0.26	4.76	0.24; 0.28	--
RES PAT	0.29	3.26	0.27; 0.31	--
EPS	1 FIX	0	--	5.2

Note: The following η-correlations were estimated: CL/F-V2/F: 0.60; CL/F-V3/F: 0.61; V2/F-V3/F: 0.57.
Abbreviations: ALAG, lag time; CI, confidence interval; CL/F, apparent clearance; CL-WT, body weight effect on clearances (exponent); CV, coefficient of variation; EPS, ε (random error); F, bioavailability; HV, healthy volunteer; IIV, inter-individual variability; KA, absorption rate constant; KA-FED, food effect on KA (coefficient); PAT, patient; Q/F, apparent inter-compartmental clearance; RES, proportional residual error; SE, standard error; V2/F, apparent central volume of distribution; V3/F, apparent peripheral volume of distribution; V-WT, body weight effect on distribution volumes (exponent).

Table S2 Summary of Demographics Across Studies

Covariate	**All Studies N=239**
Age, years, median (range)	55 (19-84)
Body weight, kg, median (range)	73.6 (42.1-165.8)
eGFR, mL/min/1.73 m^2, median (range)	77.5 (19.6-171.2)
AST, U/L, median (range)	18 (5-85)
ALT, U/L, median (range)	17 (5-138)
Sex, male, n (%)	105 (43.9)
Race, n (%)	
White	171 (71.5)
Black	23 (9.6)
Asian	38 (15.9)
Pacific Islander	1 (0.4)
Multiple/Other	4 (1.7)
Missing	2 (0.8)
Ethnicity, n (%)	
Not Hispanic	202 (84.5)
Hispanic	34 (14.2)
Missing	3 (1.3)
Disease state, n (%)	
HV	83 (34.7)
RCC	74 (31.0)
ST	21 (8.8)
VHL-RCC	61 (25.5)
Food[a], n (%)	
Fasted	239 (100)
Fed	15 (6.3)
Formulation[1], n (%)	
FFP	190 (79.5)
FMF	67 (28.0)
CYP2C19 phenotype[b], n (%)	
Poor	19 (7.9)
Intermediate	65 (27.2)
Extensive	96 (40.2)
Rapid	42 (17.6)
Ultrarapid	6 (2.5)
Missing	11 (4.6)
UGT2B17 phenotype[2], n (%)	
Poor	46 (19.2)
Intermediate	98 (41.0)
Extensive	84 (35.1)
Missing	11 (4.6)

Covariate	**All Studies N=239**
Hepatic dysfunction (NCI-ODWG), n (%)	
Normal	226 (94.6)
Mild	12 (5.0)
Moderate	1 (0.4)
Renal impairment, n (%)	
Normal	80 (33.5)
Mild	104 (43.5)
Moderate	52 (21.8)
Severe	1 (0.4)
Missing	2 (0.8)

[a]Information on food and formulation effect was obtained in crossover studies. Therefore, the numbers of patients by category can add up to more than the total number of patients, and percentages to more than 100%.
[b]The data included 10 subjects with the UGT2B17/CYP2C19 dual PM phenotype for both enzymes. All 10 were from Study 7. There were no subjects with the dual PM phenotype in the patient studies (Study 1 and Study 4).
Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CYP, cytochrome P450; eGFR, estimated glomerular filtration rate; FFP, fit-for-purpose formulation; FMF, final market formulation; HV, healthy volunteer; NCI, national cancer institute; ODWG, organ dysfunction working group; PM, poor metabolizer; RCC, (advanced) renal cell carcinoma; ST, solid tumor (advanced, besides RCC); UGT, uridine 5'-diphospho-glucuronosyltransferase; VHL-RCC, Von Hippel-Lindau disease-associated RCC

Table S3. Final SCM Result After Backward Elimination

Covariate	CL/F	V2/F	KA	F	ALAG1
Age	Yes	Yes	--	--	--
Sex	No	Yes	--	--	--
Race	No	No	--	--	--
Ethnicity	No	No	--	--	--
Disease status	No	No	--	--	--
Hepatic Dysfunction (NCI)	No	--	--	--	--
eGFR	No	--	--	--	--
Formulation	--	--	Yes	-	No
Food	--	--	--	--	Yes
UGT2B17 phenotype	Yes	--	--	Yes	--
CYP2C19 phenotype	Yes	-	-	No	-

Note: The table shows whether a covariate was found to have a significant effect on the respective parameter.
Abbreviations: ALAG1, absorption lag time; CL/F, apparent clearance, eGFR, estimated glomerular filtration rate; F, bioavailability; KA, absorption rate constant; NCI, National Cancer Institute; SCM, stepwise covariate model; V2/F, apparent central volume of distribution

Table S4. Continuous Covariate Effects on Belzutifan PK Parameters

Covariate	p5	p25	median	p75	p95
Body weight (WT) [kg]	47.9	61.5	73.6	90.1	118.4
CL/F and Q/F variation with WT [L/h]	4.26	5.01	5.63	6.41	7.65
Percent change CL/F and Q/F with WT	-24.3	-11.0	0	+13.9	+35.9
V2/F and V3/F variation with WT [L]	54.2	70.5	85.4	105.7	141.1
Percent change V2/F and V3/F with WT	-36.6	-17.4	0	+23.8	+65.3
Age [years]	26	43	55	63	74
CL/F variation with age [L/h]	7.37	6.15	5.63	5.37	5.05
Percent change CL/F with age	+31.0	+9.3	0	-4.6	-10.2
V2/F variation with age [L]	99.6	89.8	85.4	83.1	80.3
Percent change V2/F with age	+16.6	+5.2	0	-2.7	-5.9

Abbreviations: CL/F, apparent clearance; p, percentile; Q/F, apparent inter-compartmental clearance; V2/F, apparent central volume of distribution; V3/F, apparent peripheral volume of distribution; WT, body weight.

Table S5. Comparison of NONMEM and Bootstrap Estimates and CIs

Parameter	NONMEM Estimate	NONMEM 95% CI	Bootstrap Median	Bootstrap 95% CI
Fixed Effects				
CL/F (L/h)	5.63	5.25; 6.00	5.63	5.27; 5.99
V2/F (L)	85.4	80.55; 90.26	85.74	80.25; 92.56
Q/F (L/h)	5.37	3.89; 6.85	5.37	4.21; 7.16
V3/F (L)	30.38	26.42; 34.34	29.86	24.30;3 4.67
KA (/h)	2.40	2.04; 2.76	2.39	1.56; 5.92
ALAG (h)	0.16	0.16; 0.17	0.16	0.16; 0.37
KA-FED	-0.88	-1.00; -0.75	-0.88	-0.97; -0.64
CL-WT	0.65	0.45; 0.84	0.65	0.45; 0.86
V-WT	1.06	0.98; 1.14	1.05	0.96; 1.14
CL-UGT2B17 extensive metabolizers	0.39	0.24; 0.54	0.39	0.25; 0.56
CL-UGT2B17 poor metabolizers	-0.24	-0.34; -0.15	-0.24	-0.32; -0.14
CL-CYP2C19 poor metabolizers	-0.36	-0.47; -0.25	-0.36	-0.45; -0.26
F-UGT2B17 poor metabolizers	0.11	0.061; 0.16	0.11	0.060; 0.16
KA-FORM	-0.47	-0.79; -0.15	-0.42	-0.68; 1.48
V-AGE	-0.20	-0.30; -0.11	-0.20	-0.30; -0.11
CL-AGE	-0.36	-0.52; -0.20	-0.36	-0.54; -0.20
Random Effects				
IIV on CL/F	0.15	0.11; 0.18	0.14	0.11; 0.18
IIV on V2/F	0.013	0.0064; 0.019	0.012	0.0065; 0.022
IIV on V3/F	0.19	0.052; 0.33	0.20	0.070; 0.37
IIV on KA	1.15	0.78; 1.52	1.23	0.89; 2.18
Residual Error				
RES HV	0.26	0.24; 0.28	0.26	0.23; 0.28
RES PAT	0.29	0.27; 0.31	0.29	0.27; 0.31
EPS	1 FIX	--	1 FIX	--

Abbreviations: ALAG, lag time; CI, confidence interval; CL, clearance; CL-AGE, age effect on CL (exponent); CL/F, apparent clearance; CL-CYP2C19, CYP2C19 phenotype effect on CL (coefficient); CL-UGT2B17, UGT2B17 phenotype effect on CL (coefficient); CL-WT, body weight effect on clearances (exponent); CV, coefficient of variation; EPS, ε (random error); F, bioavailability; F-UGT2B17, UGT2B17 phenotype effect on F (coefficient); HV, healthy volunteer; IIV, inter-individual variability; KA, absorption rate constant; KA-FED, food effect on KA (coefficient); KA-FORM, formulation effect on KA (coefficient); NONMEM, nonlinear mixed effect modeling software; PAT, patient; Q/F, apparent inter-compartmental clearance; RES, proportional residual error; SE, standard error; V2/F, apparent central volume of distribution; V3/F, apparent peripheral volume of distribution; V-AGE, age effect on central volume of distribution (exponent); V-WT, body weight effect on distribution volumes (exponent).